trans-1,3,3,3-Tetrafluoropropylene

(CAS# 1645-83-6)

(Synonyms: 1,1,1,3-Tetrafluoropropylene; 1,3,3,3-Tetrafluoropropene; HFO-1234ze; Genetron-1234ze)

1 Introduction

trans-1,3,3,3-Tetrafluoropropylene is a non-ozone-depleting (ODP = 0) fluorocarbon with a low global warming potential (GWP = 6 for a 100 year time horizon) which has been developed as a replacement agent for ozone-depleting foam blowing chemicals (e.g., HFC-134a). As part of its consideration of exempt status for a VOC, ARB asked the Office of Environmental Health Hazard Assessment (OEHHA) to review the toxicology of trans-1,3,3,3-tetrafluoropropylene.

The American Conference of Governmental Industrial Hygienists (ACGIH) does not have a Threshold Limit Value (TLV) for worker exposure to trans-1,3,3,3-tetrafluoropropylene. The manufacturer, Honeywell International, suggests a workplace level of 1000 ppm. OEHHA notes that increased public exposure is likely if trans-1,3,3,3-tetrafluoropropylene is exempted from VOC regulation and its use becomes more widespread in California. Thus we would want to compare screening Reference Exposure Levels (REL) for trans-1,3,3,3-tetrafluoropropylene with estimated exposures from use in California.

2 Physical and Chemical Properties of trans-1,3,3,3-Tetrafluoropropylene

Description	Colorless liquefied gas; unique odor
Molecular formula	C3-H2-F4 (trans-$CHF=CHCF_3$)
Molecular weight	114 daltons
Density	1.12 g/cm^3 @ 21.1°C
Boiling point	-19ºC
Melting point	Not found
Vapor pressure	4.192 hPa @ 20ºC; 490 kPa @ 25ºC
Odor threshold	Not found
Log Pow	2.01 (estimated)
Bioconcentration factor	Not found
Solubility	0.373 g/L water
Flammability	Nonflammable
Conversion factor	4.66 µg/m^3 per ppb @ 25ºC

3 Toxicity of trans-1,3,3,3-Tetrafluoropropylene

3.1 Absorption, Distribution, Metabolism, and Excretion

Male Sprague–Dawley rats (5/concentration) were exposed to air containing 2000; 10,000; or 50,000 ppm t-1,3,3,3-tetrafluoropropylene for 6 h in a chamber (Schuster et al., 2009). Male B6C3F1 mice were also exposed to 50,000 ppm. Afterward, animals were individually housed

in metabolic cages and urines were collected at 6 or 12 h intervals for 48 h. The major metabolite (66% of total integrated 19F-NMR signals) in urine of rats exposed to 50,000 ppm was S-(3,3,3-trifluoro-trans-propenyl)-mercaptolactic acid. S-(3,3,3-Trifluoro-transpropenyl)- L-cysteine, N-acetyl-S-(3,3,3-trifluoro-trans-propenyl)-L-cysteine, and 3,3,3-trifluoropropionic acid were also present in urine of rats and mice. The major metabolite in urine of mice exposed to 50,000 ppm t-1,3,3,3-tetrafluoropropylene was thought to be an amino acid conjugate of 3,3,3-trifluoropropionic acid (18% of total integrated 19F-NMR signals). The amounts of the metabolites in urine of both mice and rats indicated that <1% of the t-1,3,3,3-tetrafluoropropylene dose was biotransformed and that 95% of all metabolites were excreted within 18 h after exposure. The authors concluded that trans-1,3,3,3-tetrafluoropropylene slowly undergoes addition–elimination with glutathione and epoxidation by cytochrome P450 (Schuster et al., 2009).

3.2 Animal Toxicity

The International Uniform Chemical Information Database (IUCLID) dataset did not list a dataset for trans-1,3,3,3-tetrafluoropropylene as of July 19, 2010. There is no file for the chemical in the Hazardous Substances Data Bank (HSDB, 2011).

Acute animal toxicity

In order to determine the LC_{50}, an acute 4-hour inhalation toxicity study was conducted with three groups of 5 male and 5 female Sprague-Dawley CD rats (Honeywell, 2010). The animals were exposed nose-only to vapors of t-1,3,3,3-tetrafluoropropylene at 0, 100,000, or 207,000 ppm. After the exposure, the animals were observed for 14 days. No deaths, no clinical signs of toxicity, and no changes in body weight or food consumption were seen. Necropsy observations were normal. There were no treatment-related or statistically significant differences in organ weights (kidneys, liver and lungs) or organ weight ratios. The 4-hour LC_{50} is greater than 207,000 ppm and the authors state that the chemical is practically nontoxic by inhalation.

In an acute cardiac sensitization study, 6 beagle dogs were exposed to vapors of t-1,3,3,3-tetrafluoropropylene at 20,000, 60,000, or 120,000 ppm (Honeywell, 2010). Exposure did not cause cardiac sensitization when the dogs were challenged with epinephrine.

Subacute animal toxicity

In a 2-week inhalation toxicity study, four groups of 5 male and 5 female rats were exposed nose only to vapors of t-1,3,3,3-tetrafluoropropylene at 0, 5000, 20,000 or 50,000 ppm for 6 h/day, 5 d/wk (10 days of exposure) (Honeywell, 2010). There were no treatment-related changes in clinical observations, body weight gain, food consumption, or food conversion efficiency. Hematologic analysis, clinical chemistry analysis, organ weight measurements, and macroscopic and microscopic examination of the heart, liver, and nasal passages showed effects in rats at 20,000 and 50,000 ppm. The main effects were the heart (muscle fiber vacuolation and mononuclear cell infiltrates) and liver (hepatocellular vacuolation and mononuclear cell infiltrates) of rats exposed to 20,000 and 50,000 ppm and in the nasal passages (decreased goblet cell expression) at 50,000 ppm. Thus 5,000 ppm was a NOEL for a 2 week exposure.

In a 4-week inhalation toxicity study five groups of male and female rats were exposed nose only to vapors of at 0, 1000, 5000, 10,000, and 15,000 ppm for 6 h/day, 5 days/week (20-21 exposure days) (Honeywell, 2010). No changes were observed by clinical observation, in body weight gain, food consumption, or food conversion efficiency. Since some variations in clinical chemistry analyses did not appear in a concentration-related pattern, the authors did not consider them to be due to treatment. Microscopic examination showed very slight to moderate inflammation of the heart in males exposed to 15,000 ppm; two males showed vacuolation of muscle fiber. Thus 10,000 ppm was a NOAEL for a 4 week inhalation exposure.

Subchronic animal toxicity

The TNO laboratory in the Netherlands exposed four groups of 10 male and 10 female rats to vapors of t-1,3,3,3-tetrafluoropropylene at 0, 1500, 5000, or 15,000 ppm for 6 h/day, 5 days/week for 13 weeks (63-64 exposure days) (TNO, 2008). No changes in clinical observations, body weight gain, food consumption, or food conversion efficiency were observed. Hematology parameters and clinical chemistry data showed some variation at 15,000 ppm (Table 1; see discussion below). At necropsy, no treatment-related gross changes were observed macroscopically; no organ weight changes were measured. Microscopic examination found multifocal mononuclear cell infiltrates in the hearts of both sexes at 15,000 ppm (Table 1). Cardiac fibrosis was not observed. Thus 15,000 ppm was the Low-Observed-Adverse-Effect Level (LOAEL) and 5,000 ppm was the No-Observed-Effect Level (NOEL) for a 13-week exposure.

Table 1. Effects after 13 week exposures of rats to t-1,3,3,3-tetrafluoropropylene (TNO, 2008)

HFO-1234ze level	0 ppm	1500 ppm	5000 ppm	15,000 ppm
Monocytes, absolute no. (10^9/L), males	0.15±0.05(10)	0.20±0.10(10)	0.14±0.06(10)	0.30±0.14(10)*
Monocytes, %, males	2.18±0.62	2.62±0.89	2.07±0.63	3.39±1.43*
Monocytes, absolute no. (10^9/L), females	0.10±0.03(10)	0.12±0.06(10)	0.18±0.07(10)	0.20±0.15(10)
Monocytes, %, females	2.56±0.65	2.50±1.05	4.00±1.75*	4.37±2.35*
Absolute uterine wt (g)	0.77±0.19(9)	0.87±0.39(10)	0.71±0.23(10)	0.52±0.09(10)*
Relative uterine wt (g/kg)	3.27±0.93(9)	3.71± 1.76 (10)	2.92±1.00(10)	2.20±0.42(10)*
Cardiac infiltrates, males	0/10	0/10	0/10	9/10*
Cardiac infiltrates, females	0/10	0/10	0/10	5/10*

Values are mean±1 SD (n) or incidence; * $p<0.05$ vs. control.

As summarized by others (e.g., Honeywell, 2010), the differences in hematology parameters, i.e. increases in thrombocytes and monocytes in male animals at 15,000 ppm and increases in hemoglobin concentration, and packed cell volume at 15,000 ppm, and in % monocytes in females at 5000 and 15,000 ppm may be treatment-related. The increases in clinical chemistry

parameters, i.e. in the enzymes aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT0 and in urea in the plasma of males at 15,000 ppm, and in glucose, urea, inorganic phosphate, and potassium in females at 15,000 ppm, may be treatment-related. The decrease in the absolute and relative weight of the uterus in females at 15,000 ppm was considered to be due to estrous cycle-related uterus weight variations rather than to HFO-1234ze exposure. Other changes in absolute or relative organ weights were not detected. Macroscopic examination did not show exposure-related gross pathology. OEHHA staff used the increase in cardiac infiltrates at 15,000 as the LOAEL of the critical endpoint to develop a screening chronic REL.

Chronic toxicity in animals

No data were located.

Developmental and reproductive toxicity in animals

Groups of 24 mated female rats were exposed nose only to 0, 1500, 5000, or 15,000 ppm of t-1,3,3,3-tetrafluoropropylene for 6 h/day on gestation days (gd) 6-19/20 (TNO, 2007). No animals died and there were no effects on body weight or food consumption; clinical observations were normal. There were no significant differences in fecundity index, number of corpora lutea, number of implantation sites, number of live fetuses, post implantation loss, or sex ratio. In the pups, there was a higher incidence of observations of delayed ossification in controls compared to the rats exposed to 1,3,3,3-tetrafluoropropylene, an example of random variation. The NOAEL was 15,000 ppm.

In order to determine appropriate concentrations for a definitive study of prenatal developmental toxicity, a range-finding study was conducted with four groups of time-mated New Zealand does (6/group) exposed whole-body to 0, 1500, 5000, or 15,000 ppm 1,3,3,3-tetrafluoropropylene for 6 hours/day during gd 6-28 (WIL, 2008). All animals survived to gd 29. No signs of maternal toxicity were observed. Intrauterine growth and survival were not affected by maternal exposure at any level (Table 2). No external fetal malformations or developmental variations were found. The authors concluded that inhalation up to 15,000 ppm 1,3,3,3-tetrafluoropropylene by pregnant rabbits did not cause maternal or developmental toxicity.

Table 2. Fetal rabbit parameters as a function of concentration in range-finding study

HFO-1234ze	0 ppm	1500 ppm	5000 ppm	15,000 ppm
Gravid does	5	6	6	6
Live fetuses	41	57	50	45
Dead fetuses	0	0	0	0
Fetuses/doe	8.2	9.5	8.3	7.5
Post-implantation losses	1	2	3	2
Fetal weight (g)	42.7 ± 5.65*	39.1 ± 3.83	42.3 ± 3.68	41.8 ± 5.37

*mean ± 1 SD

In a prenatal developmental toxicity study, four groups of 22 time-mated female New Zealand rabbits (5-6 months old) were exposed whole-body to 0, 4000, 10,000, or 15,000 ppm 1,3,3,3-tetrafluoropropylene for 6 h/day during gd 6 to 28 (Huntingdon, 2010). All animals survived to

necropsy on gd 29. No signs of maternal toxicity were observed. Intrauterine growth and survival were unaffected by maternal exposure to all exposure levels (Table 3). The authors concluded that inhalation exposures of pregnant rabbits up to 15,000 ppm did not cause maternal toxicity. There were no effects on pup live birth or sex ratio, no external malformations, and no developmental effects in internal organs. The NOEL was 15,000 ppm.

Table 3. Fetal rabbit parameters as a function of concentration in developmental study

HFO-1234ze	0 ppm	4000 ppm	10,000 ppm	15,000 ppm
Mated does	22	22	22	22
Pregnant does	20	16	17	20
Dead fetuses	0	0	0	0
Live fetuses examined	166	149	161	172
Fetuses/pregnant doe	8.4	9.3	9.5	8.6
Fetal weight (g)	41.5 ± 4.26*	40.2 ± 3.71	39.9 ± 4.18	41.4 ± 4.23

*mean ± 1 SD

Mutagenicity and carcinogenicity

Mutagenicity tests reported in Honeywell's Toxicologic Summary (Honeywell, 2010) were uniformly negative.

An Ames assay screen was conducted with the bacteria *Salmonella typhimurium* (strains TA1535, TA1537, TA98, and TA100) and *Escherichia coli* (strain WP2 uvrA), both with and without metabolic activation from a rat liver S9 preparation, at 50,000 ppm t-1,3,3,3-tetrafluoropropylene (Japan Bioassay Research Center, 2009). There was no mutagenic activity.

A Good Laboratory Practices (GLP) Ames assay was conducted with t-1,3,3,3-tetrafluoropropylene which involved exposure of strains TA 1535, TA1537, TA 98, TA 100 and WP2 uvrA, both with and without S-9 metabolic activation. Exposure levels were up to 760,000 ppm (plus 19% O_2 and 5% CO_2). There was no mutagenic activity.

A GLP Chromosome Aberration (CA) Test was conducted with cultured human lymphocytes that were exposed to vapors of t-1,3,3,3-tetrafluoropropylene up at 10%, 20%, 40%, 60%, and 76% (760,000 ppm), both with and without S-9 metabolic activation (TNO, 2005). There was no clastogenic activity. However, the compound was cytotoxic at 40% and 60%. Structural chromosome aberrations were induced by the positive control (25 μg/ml cyclophosphamide)

A mouse Micronucleus (MN) Assay was conducted following a single 4-hour exposure to 29,208 ppm t-1,3,3,3-tetrafluoropropylene. At 48 and 72 hours after exposure, peripheral blood smear samples were obtained from 5 male and 5 female exposed mice, as well as from negative and positive control animals. The authors concluded that a 4-hour exposure to 29,208 ppm did not cause chromosome damage in the peripheral blood of exposed mice.

A second mouse Micronucleus Assay was conducted with 10 male and 10 female CD-1 mice exposed nose-only to 103,300 ppm t-1,3,3,3-tetrafluoropropylene for 4 h (Huntington, 2004). At 24- and 48-hours after exposure, bone marrow cells from 5 mice per sex per interval were

collected and analyzed for micronuclei. Micronuclei were not increased in either normochromatic or polychromatic erythrocytes and there was no evidence of bone marrow cell toxicity. Micronuclei were increased in the positive control (40 mg/kg cyclophosphamide).

A rat Micronucleus Test was an added procedure to the 4-week inhalation toxicity study described above. At necropsy, bone marrow from male rats in the control, 5,000, 10,000, or 15,000 ppm groups was used in the Micronucleus Test. At 15,000 ppm, there was no damage to chromosomes or no increase in micronuclei in the bone marrow cells.

An Unscheduled DNA Synthesis (UDS) Test was also included in the 4-week inhalation toxicity study described above. At necropsy, liver cells from male rats in the control, 5,000 and 15,000 ppm groups were used for the test. At the highest concentration tested (15,000 ppm), no UDS was observed in the liver cells.

Carcinogenicity has not been tested directly in a lifetime bioassay. However, at the Hamner Institutes (formerly Chemical Industry Institute of Toxicology Centers for Health Research), Thomas et al. (2009) used gene expression profiles (microarrays) from animals exposed for 13 weeks to predict the increased incidence of mouse lung tumors at 2 years (life-time) of exposure. Animals were exposed for 13 weeks to a total of 26 diverse chemicals, both carcinogens and non-carcinogens based on 2 year tests, with matched vehicle controls. The entire study lasted 3 years. Unfortunately, significant batch-related effects were observed. However, adjustment for batch effects significantly improved the ability to predict increased lung tumor incidence. For the best statistical model, the estimated predictive accuracy under honest fivefold cross-validation was 79.3% with a sensitivity (identified accurately the known carcinogens) and specificity (detected accurately the known noncarcinogens) of 71.4 and 86.3%, respectively. Similar studies were done for female mouse liver (Thomas et al., 2001) and male rat kidney.

Using this approach for three sites (female mouse lung and liver, and male rat kidney) (Thomas, 2007; Thomas, 2009; Honeywell, 2010) female B6C3F1 mice and male F344 rats were exposed by inhalation to 2000 and 10,000 ppm t-1,3,3,3-tetrafluoropropylene 6 h/day, 5 days/week for 13 weeks. Microarray analyses were carried out on the three organs and compared to known carcinogens and noncarcinogens. The statistical classification analysis) predicted that t-1,3,3,3-tetrafluoropropylene would be noncarcinogenic in both female mouse liver and male rat kidney. A positive response was predicted for the female mouse lung. These findings had a statistical probability of selecting true negatives of 100% for kidney, 99.2% for liver and 83% for lung. The probability for a true positive being identified was 90% for the kidney, 97.2% for the liver, and only 71.3% for the lung. This classification analysis will require thorough peer-review to determine its reliability. The authors believe that the predicted mouse lung tumors due to t-1,3,3,3-tetrafluoropropylene have minor relevance to human tumors.

According to Honeywell, the weight of evidence suggests that t-1,3,3,3-tetrafluoropropylene is not likely to be carcinogenic. Their conclusion is supported by the lack of mutagenic activity in all mammalian and bacterial cell studies, the lack of significant metabolic activity, the lack of systemic toxicity, and the lack of significant lesions in the livers, kidneys, and lungs in any of the studies. However, there were systemic lesions in the heart.

3.3 Human Toxicity

No data on human toxicity were located.

4 Derivation of Screening Acute REL (1-hour exposure)

Study	Honeywell (2010)
Study population	Male and female Sprague-Dawley CD rats (5/sex/group)
Exposure method	Inhalation of 0; 100,000; or 207,000 ppm
Exposure duration	4 hours (once) plus 14 day observation
Critical effects	none
LOAEL	none
NOAEL	207,000 ppm
Extrapolation to 1 hour	328,000 ppm ($207{,}000^3$ x 4 h = C^3 x 1 h)
LOAEL uncertainty factor	1 (NOAEL observed)
Interspecies uncertainty factor	
Toxicokinetic $UF_{A\text{-}k}$	2 (default)
Toxicodynamic $UF_{A\text{-}d}$	√10 (default)
Intraspecies uncertainty factor	
Toxicokinetic $UF_{H\text{-}k}$	10 (default)
Toxicodynamic $UF_{H\text{-}d}$	√10 (default)
Database uncertainty factor	1 (developmental study available)
Cumulative uncertainty factor	200
Acute Reference Exposure Level	1600 ppm (7500 mg/m^3)

Acute Reference Exposure Levels (aRELs) are levels at which intermittent one-hour exposures are not expected to result in adverse health effects (see Section 5 of the Technical Support Document (TSD) (OEHHA, 2008).

The screening acute REL for trans-1,3,3,3-tetrafluoropropylene is based on an LC_{50} study in which male and female rats were exposed for 4 h on day 1 and observed for 14 days for any after-effects. There were no clinical signs of toxicity or changes in body weight during the exposure or during the 14 day observation period. The screening acute REL was developed using recently approved methodology (OEHHA, 2008). The methodology was modified from earlier methodology due to a mandate to specifically insure that infants and children are protected from the adverse effects of chemicals.

Because of the limited data available on trans-1,3,3,3-tetrafluoropropylene, default values were used for the uncertainty factors (UF). The default interspecies $UF_{A\text{-}k}$ of 2 was used for residual toxicokinetic differences in studies of non- primate species using the human equivalent concentration (HEC) approach. In this case the HEC adjustment factor was 1 since most adverse effects of the chemical are systemic. The default interspecies $UF_{A\text{-}d}$ of √10 was applied to compensate for the absence of data on pharmacodynamic differences between rodents and humans. The default intraspecies $UF_{A\text{-}k}$ of 10 was used since there was no information on trans-

1,3,3,3-tetrafluoropropylene metabolism at different stages of human development. The default interspecies UF_{A-d} of √10 was applied to compensate for the absence of data on pharmacodynamic differences among humans to the effects of trans-1,3,3,3-tetrafluoropropylene.

5 Derivation of Screening Chronic Reference Exposure Level (REL)

Study	TNO, 2008
Study population	Groups of 10 male and female SD rats
Exposure method	Inhalation of 0, 1500, 5000, or 15,000 ppm
Exposure duration	8 h/day, 5 days/week for 13 weeks
Critical effects	multifocal mononuclear cell infiltrates of the heart (Table 1)
LOAEL	15,000 ppm
NOAEL	5000 ppm
Benchmark Concentration (BMC_{05})	data not appropriate
Average experimental exposure	1190 ppm at NOAEL (5000 ppm x 8/24 x 5/7)
Human equivalent concentration	1190 ppm at NOAEL (gas with systemic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h))
Subchronic uncertainty factor	√10
LOAEL uncertainty factor	1
Interspecies uncertainty factor	
Toxicokinetic UF_{A-k}	2 (default)
Toxicodynamic UF_{A-d}	√10 (default)
Intraspecies uncertainty factor	
Toxicokinetic UF_{H-k}	10 (default)
Toxicodynamic UF_{H-d}	√10 (default)
Database uncertainty factor	1(developmental study available)
Cumulative uncertainty factor	600
Chronic REL	2 ppm (9 mg/m^3; 9,000 μg/m^3)

The chronic Reference Exposure Level (cREL) is a concentration at which effects are not expected from chronic exposures to trans-1,3,3,3-tetrafluoropropylene (see Section 7 in the TSD (OEHHA, 2008)).

The default interspecies UF_{A-k} of 2 was used for residual toxicokinetic differences in studies of non-primate species using the human equivalent concentration (HEC) approach. In this case the HEC adjustment factor was 1 since heart infiltrates occur internally. The default interspecies UF_{A-d} of √10 was applied to compensate for the absence of data on pharmacodynamic differences between rodents and humans. The default intraspecies UF_{A-k} of 10 was used since there was no information on metabolism at different stages of human development. The default interspecies UF_{A-d} of √10 was applied to compensate for the absence of data on pharmacodynamic differences among humans to the effects of trans-1,3,3,3-tetrafluoropropylene.

6 Data Gaps

Data gaps of concern to OEHHA staff include:

1. No lifetime inhalation study of trans-1,3,3,3-tetrafluoropropylene is available. The longest inhalation study available is a 13 week (subchronic) study with relatively small groups of only one strain (Sprague-Dawley) of one species (rats). This is a serious data gap for a potentially high production volume chemical.

2. A substantial developmental toxicity study with group sizes of 22 pregnant female rabbits was reported, but no multigenerational studies or other investigations addressing reproductive toxicity in either sex were available.

3. There are no data in neonatal animals of the effects of trans-1,3,3,3-tetrafluoropropylene exposure. OEHHA has a mandate to determine if our health values adequately protect infants and children.

7 Conclusion

There are no direct carcinogenicity or long-term toxicity data on trans-1,3,3,3-tetrafluoropropylene.

Exposure to workers and the general public near facilities in California using trans-1,3,3,3-tetrafluoropropylene will occur if it is exempted. The proposed screening acute REL of 7500 mg/m^3 (1600 ppm) and chronic REL of 9 mg/m^3 (2 ppm) are expected to be protective of possible adverse health effects.

8 References

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